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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,764	CHADDOCK ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-40* is/are pending in the application.

4a) Of the above claim(s) *31-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 March 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/12/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendment

1) Acknowledgment is made of Applicants' preliminary amendment 03/12/02. With this, Applicants have submitted an abstract.

Election

2) Acknowledgment is made of Applicants' election filed 11/04/04, with traverse, of invention I, claims 22-30 and 37-40, in response to the written lack of unity mailed 10/04/04. Applicants' contend that the application was considered to have unity of invention during the international phase. Applicants state that since a search and examination has already been carried out during the international phase, it would place absolutely no burden to examine all of the present claims.

Applicants' arguments have been carefully considered, but are non-persuasive. The lack of unity under PCT Rule 13.1 and 13.2 is based on whether or not the special technical feature of an invention defines over the prior art. It does not depend on whether or not a search and examination has already been carried out during the international phase. As set forth previously, the special technical feature of the first claimed method is a method of reducing toxicity of a clostridial toxin derivative preparation by contacting with a ligand. The special technical feature of inventions II, III and IV are an affinity chromatography column comprising a ligand that selectively binds to toxin, but not to the toxin derivative; a clostridial toxin derivative preparation comprising 1-100 ppm clostridial toxin per toxin derivative; and a composition comprising a clostridial toxin derivative, a pharmaceutically acceptable carrier and a ligand that selectively binds to the toxin respectively. However, these special technical features do not define over the prior art, since the prior art already taught the method, the column and the preparation. For instance, Gimenez *et al.* (*J. Protein Chem.* 12: 351-363, 1993 – Applicants' IDS) taught a method of contacting a type A clostridial neurotoxin contained in a buffer and digested with pepsin (i.e., a clostridial toxin derivative preparation) with cationic DEAE-Sephadex or Mono Q in a column wherein the 42K fragments (i.e., toxin derivatives) did not bind to DEAE-Sephadex or Mono Q, but the 147 kD toxin did bind (see sections 3.3 and 2.5; Figure 3; and paragraph bridging pages 358 and 359). Gimenez *et al.* taught the chromatographically purified clostridial neurotoxin fragments (i.e., derivatives) that were dialyzed, ammonium sulfate-precipitated, and further dialyzed to obtain purified fragments (see

section 3.5). The chromatographic elution results depicted in Figure 5D show that the toxin fragments were free of the 147 kD toxin. Therefore, inventions I, II, III and IV do not share significant reagents or compositions, and/or methods steps. Therefore, the lack of unity held in the instant application is proper and is hereby made FINAL.

Status of Claims

3) Claims 1-21 have been canceled via the amendment filed 03/12/02.

New claims 22-40 have been added via the amendment filed 03/12/02.

Claims 22-40 are pending.

Claims 31-36 have been withdrawn from consideration as being directed to a non-elected invention or a non-elected species. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Elected claims 22-30 and 37-40 are under examination. A First Action on the Merits on these claims is issued.

Information Disclosure Statements

4) Acknowledgment is made of Applicants' information disclosure statement filed 03/12/02 and 12/18/02. The information referred to therein has been considered and a signed copy is attached to this Action.

Priority

5) The instant application is national stage 371 application of PCT/GB00/03519 filed 09/13/00 and claims foreign priority to application 9921592.3 filed 09/13/99 in United Kingdom.

It is noted that a certified copy of the foreign priority document 2000/17052 has been submitted to the Office on 03/12/02.

Specification - Informalities

6) The instant specification is objected to for the following reason(s):

(A) The instant application is informal in the format or arrangement of the specification. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the Applicants' use.

Content of Specification

(a) Title of the Invention: See 37 C.F.R 1.72(a). The title of the invention should be placed at the top of the first page of the specification. It should be brief but

technically accurate and descriptive, preferably from two to seven words.

(b) Cross-References to Related Applications: See 37 C.F.R 1.78 and M.P.E.P § 201.11.

(c) Statement Regarding Federally Sponsored Research and Development: See M.P.E.P § 310.

(d) Reference to a "Microfiche Appendix": See 37 C.F.R 1.96(c) and M.P.E.P § 608.05. The total number of microfiche and the total number frames should be specified.

(e) Background of the Invention: The specification should set forth the Background of the Invention in two parts:

(1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."

(2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."

(f) Brief Summary of the Invention: A brief summary or general statement of the invention as set forth in 37 C.F.R 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

(g) Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 C.F.R 1.74.

(h) Detailed Description of the Invention: A description of the preferred embodiment(s)

of the invention as required in 37 C.F.R 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. This item may also be titled "Best Mode for Carrying Out the Invention." Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.

(i) Claim or Claims: See 37 C.F.R 1.75 and M.P.E.P § 608.01(m). The claim or claims must commence on separate sheet. (37 C.F.R 1.52(b)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps.

(j) Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single paragraph of 250 words or less on a separate sheet following the claims.

(k) Drawings: See 37 C.F.R 1.81, 1.83-1.85, and M.P.E.P § 608.02.

(l) Sequence Listing: See 37 C.F.R 1.821-1.825.

(B) To be consistent with the drawings for Figures 1A and 1B, at line 3 of page 12 of the specification, Applicants should refer to 'Fig. 1' as --Figures 1A and 1B--.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

7) Claim 37 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 37 includes the limitations: 'first treated preparation' and 'second treated preparation'. However, there appears to be no descriptive support for the above-identified

limitations in the specification as originally filed. Therefore, the limitations in the claim are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or to point to specific pages and line numbers in the originally filed specification where support for such recitations can be found.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

8) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

9) Claims 22-30 and 37-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 22, 26, 27 and 37 are vague and indefinite in the limitation: 'derivative', because it is unclear what is encompassed in this limitation. What constitutes a derivative, and how much of the clostridial toxin's original structure has to be retained such that the resulting product can be considered a 'derivative' is not clear. The metes and bounds of the structure encompassed in the limitation 'derivative' are indeterminate.

(b) Claims 23 and 24 are vague and indefinite in the limitation: 'an Hc portion', because it is unclear what is encompassed in this limitation. What constitutes an Hc portion, and how much of the clostridial toxin's original structure or how much of the clostridial toxin's carboxy terminal region has to be retained such that the resulting product can be considered an 'Hc portion' is not clear. The metes and bounds of the structure encompassed in the limitation 'an Hc portion' are indeterminate.

(c) Claims 29 and 30 are vague and indefinite in the limitation: 'an LH_N fragment', because it is unclear what is encompassed in this limitation. What constitutes an LH_N fragment, and how much of the clostridial toxin's original structure or how much of the clostridial toxin's amino terminal region has to be retained such that the resulting product can be considered as an 'LH_N

fragment' is not clear. The metes and bounds of the structure encompassed in the limitation 'an LH_N fragment' are indeterminate.

(d) Claim 22 has improper antecedence in the limitation 'the toxin' (see line 3), because there is no earlier recitation of any toxin in the claim. Claim 22 is vague and confusing in the limitation 'the toxin' (see line 3) because it is unclear what toxin Applicants are referring to? It is not clear whether this is a clostridial toxin, non-clostridial toxin, or contaminant endotoxin?

(e) Claims 23-26 are vague and confusing in the limitation 'the toxin' (see line 2) because it is unclear what toxin Applicants are referring to? It is not clear whether this is a clostridial toxin, non-clostridial toxin, or a contaminant endotoxin?

(f) Claims 23-25 are broadening in scope in the limitation 'binds', because claims 23-25 depend from claim 22, wherein the ligand is recited as the one which 'selectively binds', as opposed to a ligand which 'binds' non-selectively.

(g) Claim 22 has improper antecedence in the limitation: 'the toxin derivative' (see last line), because the earlier recitation in the claim is of 'a clostridial toxin derivative preparation', but not of a generic toxin derivative. For proper antecedence, it is suggested that Applicants replace the limitation with --the clostridial toxin derivative--.

(h) Claim 30 is confusing in the recitation: 'a targeting ligand'. Claim 30 depends from claim 22, which includes the limitation: 'a ligand'. It is unclear how 'a targeting ligand' differs in structure and/or scope from 'a ligand'.

(i) Claim 37 has improper antecedence in the limitation: 'the derivative' (see lines 4 and 7), because the earlier recitation in the claim is of a derivative of a clostridial toxin, but not of a generic derivative. For proper antecedence, it is suggested that Applicants replace the limitation with --the clostridial toxin derivative--.

(j) Claim 37 is confusing in the limitation: 'separating the first ligand from the preparation to obtain a first treated preparation; contacting the first treated preparation with a second ligand which binds to the first ligand'. Since the first ligand is recited as already separated, it is unclear how the second ligand can bind to the first ligand in the first treated preparation.

(k) Claims 23-30 and 38-40, which depend directly or indirectly from claim 22 or 37, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in

the base claim.

Rejection(s) under 35 U.S.C. § 102

10) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11) Claims 22-24 and 27-29 are rejected under 35 U.S.C. § 102(b) as being anticipated by Rossetto *et al.* (*Biochem. J.* 285: 9-12, 1992).

Rossetto *et al.* taught a method of removing a clostridial toxin, tetanus toxin, from protein samples or an L-chain-containing tetanus toxin sample by applying the samples to a chelating Superose HR 10/2 column charged with the ZnCl2 ligand. The tetanus toxin comprising the H_C portion selectively binds to immobilized metal ion affinity column whereas the L-H_N fragment or the L chain does not and therefore is eluted out, i.e., separated from the ligand (see title; abstract; pages 10 and 11; and Figures 4 and 2). Rossetto *et al.* expressly taught that the method can be extended to the botulinum neurotoxins (see abstract).

Claims 22-24 and 27-29 are anticipated by Rossetto *et al.*

Rejection(s) under 35 U.S.C. § 103

12) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

13) Claims 25 and 26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rossetto *et al.* (*Biochem. J.* 285: 9-12, 1992) as applied to claim 22 above, and further in view of Hallis *et al.* (*In: Botulism and Tetanus Neurotoxins.* (Ed) DasGupta BR *et al.* Plenum Press, New York, pages 433-436, 1993).

The teachings of Rosetto *et al.* are explained above which do not teach the ligand to be an antibody that binds to the clostridial toxin or a preparation with a plurality of antibodies which selectively bind the toxin but not the toxin derivative.

However, an antibody that binds to the clostridial botulinum toxin or a plurality of antibodies which selectively bind the toxin but not the toxin derivative were known in the art at the time of the invention. For instance, Hallis *et al.* taught a monoclonal antibody, 5BA 2.3, 5BA 3.3, 5BA 4.3 and 5BA 9.3, which binds to the botulinum toxin, but not to the LH_N toxin fragment or derivative (see Table 2) and a preparation comprising a plurality of these antibodies (see Table 3).

Given that monoclonal antibodies can be advantageously produced in large quantities using Hallis' hybridoma, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was to use Rosetto's method with the metal ligand replaced with Hallis' antibody ligand or Hallis' plurality of antibodies to separate a botulinum toxin from an LH_N toxin fragment or derivative to produce the method of the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of extending Rosetto's method to separate botulinum toxin from its derivative since Rosetto *et al.* expressly taught that their method is extendable to the separation of botulinum toxins. Replacement of one affinity ligand with another, art-known ligand, such as, Hallis' botulinum-specific antibodies or antibody ligand, is routine and conventional, is well within the realm of routine experimentation, would have been obvious to a skilled artisan, and would have brought about similar results or effects.

Claims 25 and 26 are *prima facie* obvious over the prior art of record.

Remarks

14) Claims 22-30 and 37-40 stand rejected.

15) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions

24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of after-final amendments is (571) 273-8300.

16) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

January, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER